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Nitrogen Protecting Groups: Recent Developments and New Applications

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1. Introduction

The chemical manipulations of complex polyfuntional molecules often require the sequential protection and deprotection of the various functionalities. The introduction and removal of a protecting group demands careful synthetic planning in order to achieve the required degree of orthogonality among the protective groups present in a molecule.

The challenge of designing new nitrogen protecting groups that are stable to a wide range of reaction conditions, are readily available, and are easily removed under mild reaction conditions continues to attract a great deal of attention in a wide range of chemical fields such as peptide, nucleoside, and polymer synthesis, as well as the construction of combinatorial libraries. Historically, the value of a given nitrogen protective group was measured by some of the qualities just mentioned, as well as by its ability to protect a nitrogen functionality without affecting either the chemical nature of the molecule or the outcome of the chemical reaction. In recent years, a number of nitrogen protecting groups have been used as chiral auxiliaries, adding a new dimension, stereochemical control, to the traditional role that the nitrogen protective group plays in organic chemistry. Because of the large volume of work in this area, and its significance in the field of asymmetric synthesis, we have devoted an entire section to this topic.

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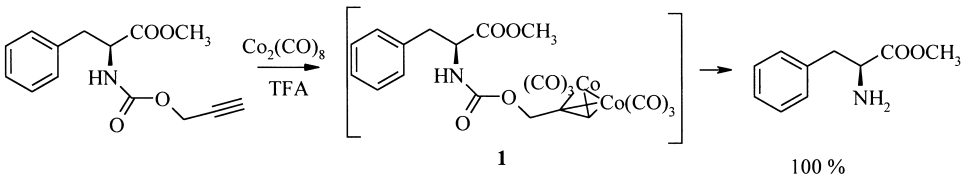
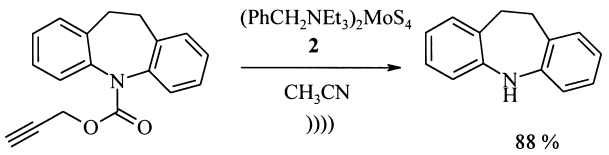


Scheme 1.



Scheme 2.

The first part of this review will discuss new nitrogen protecting groups reported in 1998 and the first half of 1999. The remainder of the report will discuss new developments and applications of known nitrogen protective groups in areas of chemistry such as polyamines, stereochemical control, and nitrogen deprotection.

2. New Nitrogen Protecting Groups

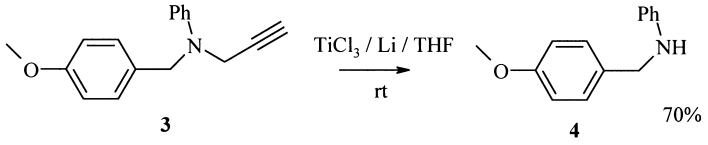
Though the allyl group has been widely used as a nitrogen protecting group,[1,2] either directly bonded to the nitrogen or as allyloxy carbamates (alloc), the propargyl group has been less extensively investigated. The 1,1-dimethyl-2-propynyloxycarbonyl group (DMPOC) was reported to be a useful protecting group for sulfur-containing peptides, and was removed by hydrogenolyses with 5% Pd/C in moderate yields.[3] Several reports have recently appeared in the literature describing new uses of propargyl carbamate as a nitrogen protecting group. Propargyl chloroformate was used to introduce the propargyloxycarbonyl (Proc) on a variety of amino groups.[4,5] A number of different approaches were used for the removal of the protecting group. In one instance, the propargyloxycarbonyl, which is stable to neat trifluoroacetic acid (TFA), was readily cleaved with $Co_2(CO)_8$ and TFA at room temperature (Scheme 1).[4] Deprotection of the Proc group was achieved with, or without, the isolation of the alkyne–Co complex **1**.

The Proc group was also readily removed when sonicated (ultrasonic cleaning bath, 25°C, 0.75 h), in the presence of tetrathiomolybdate **2** in acetonitrile (Scheme 2). In the absence of ultrasound, the reaction did not go to completion.[5]

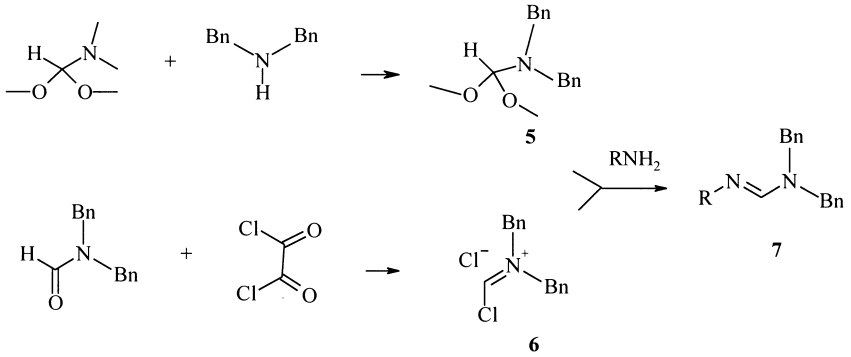
A number of amides,[6] as well as primary and secondary amines[7] were protected with the propargyl group directly attached to the nitrogen. For instance, the propargyl group in compound **3** was removed with a low valent titanium reagent (LVT), such as $TiCl_3$/Li/THF, without affecting the alkyloxy group present in the molecule, to give the corresponding secondary amine **4** in 70% yield (Scheme 3).[7]

Also described recently was the use of *N*,*N*-dimethyl, and *N*,*N*-dibenzyl formamidine as primary amine protecting groups.[8] *N*,*N*-dibenzyl formamidines **7** are stable in moderately acidic and basic media, and can be prepared from either dibenzyl formamide acetal **5** or *N*,*N*-dibenzyl chloromethylene iminium chloride **6** (Scheme 4).[9]

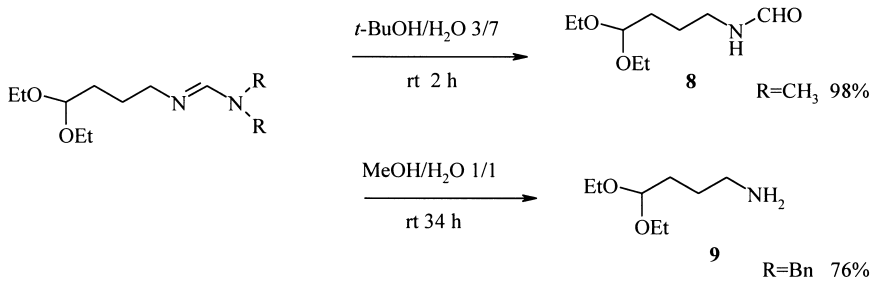
The *N*,*N*-dimethyl and *N*,*N*-dibenzyl formamidine protecting groups can be removed either by hydrolysis or



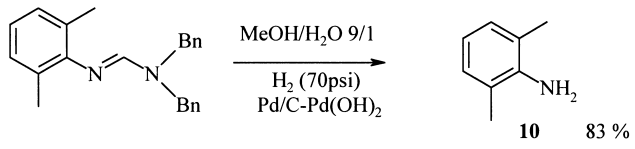
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

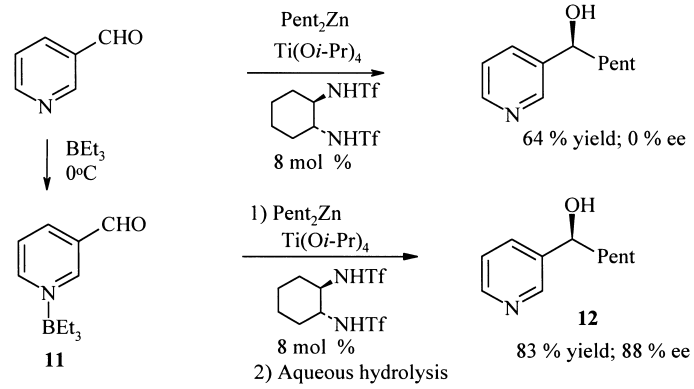
hydrogenolysis. In the case of *N*-alkyl-*N*′*N*′-dimethylformamidines, neutral hydrolysis resulted in the formation of the corresponding formamide **8**, whereas the corresponding dibenzyl analogs gave the primary amine **9** (Scheme 5).

Both *N*-alkyl *N*′*N*′-dialkyl and benzyl formamidines resulted in a mixture of alkylamine and *N*-methyl alkylamine under hydrogenolysis conditions. Aryl formamidines required basic hydrolysis conditions to give the corresponding primary amine. Unlike their *N*-alkyl analogs, hydrogenolysis of the *N*-aryl *N*′*N*′-dibenzyl formamidines resulted in excellent yields of the primary amine **10** (Scheme 6).

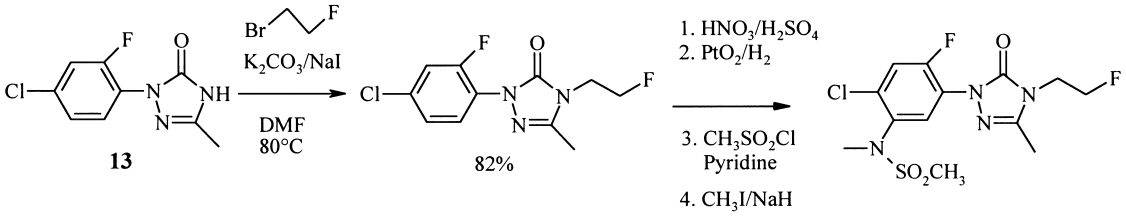
Even though there are several reports of the use of metals to protect nitrogen through chelation,[10] this approach has not found extensive application in this field. This strategy was successfully applied, however, after initial attempts failed to prepare chiral pyridyl alcohols with chiral catalysts. Failure to attain the high stereoselectivity expected from these reactions was attributed to the strong coordination of the amino function and the titanium metal, which results in deactivation of the chiral catalyst and nonasymmetric addition.

As shown in Scheme 7, addition of BEt_3 at 0°C in ether to form the intermediate pyridine–BEt_3 complex **11** dramatically altered the outcome of these reactions. (*S*)-1-(3′-Pyridyl)hexanol **12** was obtained in 83% yield and 88% ee using the pyridine–BEt_3 complex.[11]

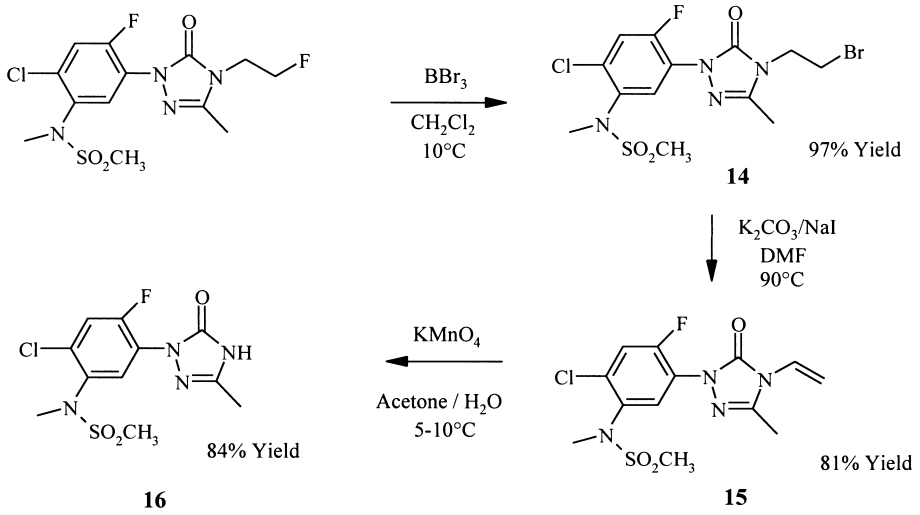
The high stability of alkyl fluorides, such as 2-fluoroethyl, to a wide range of reaction conditions has recently been exploited in the design of a new nitrogen protecting group. It was found that the 2-fluoroethyl group was stable to nitration under strong acidic conditions, catalytic hydrogenation, and alkylation under basic conditions. The 2-fluoroethyl group was readily introduced, in good yields, from the reaction of compound **13**, 1-bromo-2-fluoroethane, potassium carbonate, and sodium iodide (Scheme 8).



Scheme 7.



Scheme 8.



Scheme 9.

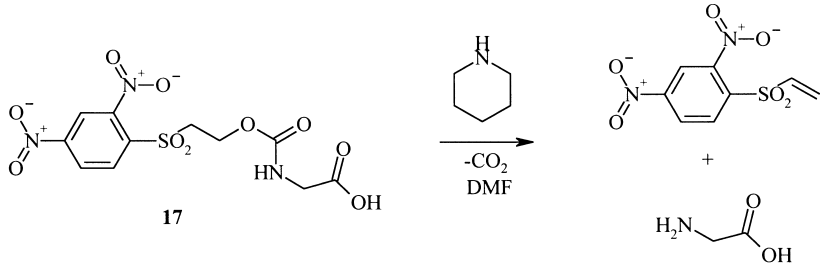
Deprotection of the 2-fluoroethyl protecting group was achieved in three steps. The first step involving halogen exchange with BBr_3, at 10°C, was fast, and produced the corresponding *N*-2-bromoethyl derivative **14**. Dehydrobromination, followed by oxidation of *N*-vinyl derivative **15** with potassium permanganate, gave the deprotected material **16** (Scheme 9).[12]

A number of 2-arylsulfonylethoxycarbonyl nitrogen protecting groups, which are removed by a base catalyzed β-elimination procedure and could be used as alternatives to 9-fluorenylmethyloxycarbonyl (fmoc), had been previously reported.[13–15] More recently Ramage and co-workers[16] found the 2-(4-nitrophenyl) sulfonylethoxycarbonyl (Nsc) to be a useful alternative base labile nitrogen protecting group to fmoc for amino acids in solid phase peptide synthesis (SPPS). The Nsc group had both a moderate absorption at 380 nm, which is important for real-time monitoring of the deprotection process, and a decrease in the rearrangement of X-Asp, a serious problem in SPPS. Also recently published was the synthesis of the chloroformate reagent 2-(2,4-dinitrophenylsulfonyl)ethyloxycarbonyl chloride.[17] This reagent was used to introduce the base labile amino protecting group 2-(2,4-dinitrophenylsulfonyl)ethoxycarbonyl ($DNPSO_2EOC$) for peptide synthesis. No racemization was observed during protection, deprotection or coupling. Deprotection, which was achieved by the treatment of compound **17** and piperidine, could be monitored spectrophometrically at 350 nm (Scheme 10).

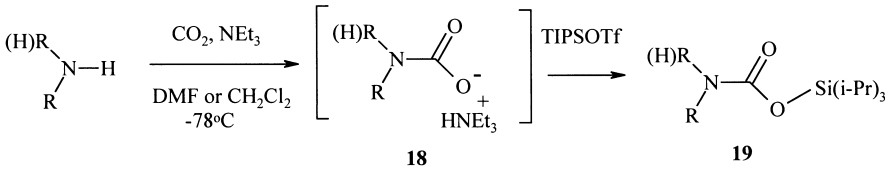
The synthesis, and nitrogen protecting group use, of a new silyl carbamate, triisopropylsilyloxycarbonyl (Tsoc), has recently been described.[18] The *N*-Tsoc derivatives were prepared directly from the corresponding primary or secondary amine, triethylamine, and dry CO_2 gas, or dry ice, in DMF at −78°C to give the intermediate carbamic acid salt **18**. The carbamic acid salt is treated with triisopropylsilyl triflate (TIPS-OTf) to give the corresponding *N*-protected material **19** (Scheme 11). Reported yields ranged from excellent to moderate, the moderate yields were obtained with anilines having strong withdrawing groups. Hydroxyl groups present did not require prior protection. The Tsoc group was found to be stable to trifluoroacetic acid, catalytic hydrogenation over Pd/C in acetic acid, and morpholine, making the deprotecting step orthogonal to Boc, Cbz, and Fmoc carbamates.

The *N*-Tsoc group in compound **20** was cleaved when treated with tetrabutylammonium fluoride (TBAF) in THF at 0°C (Scheme 12), to give the corresponding primary amine **21** in 91% yield. Hydroxyl group protection was not necessary.

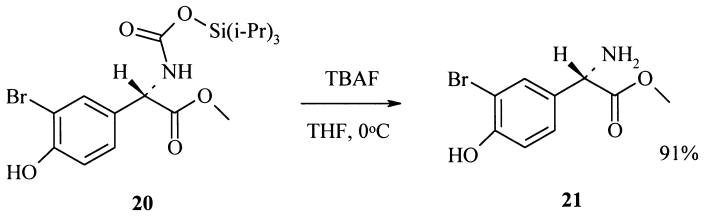
A new strategy for linking protected amino carbonyl compounds to solid supports was recently developed.[19] The ability of the 9-phenylfluorene-9-yl (PhF) amine protecting group to both prevent racemization of α-amino carbonyl compounds, by sterically shielding the α-proton,[20a] and provide higher stability to acid solvolysis



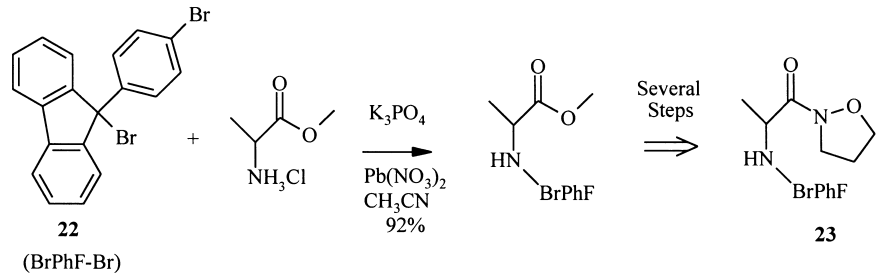
Scheme 10.



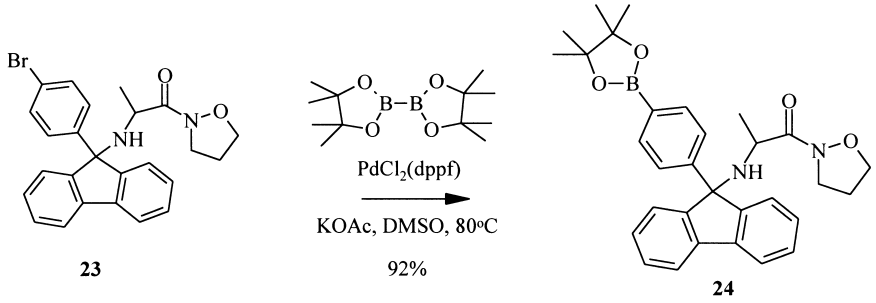
Scheme 11.



Scheme 12.



Scheme 13.



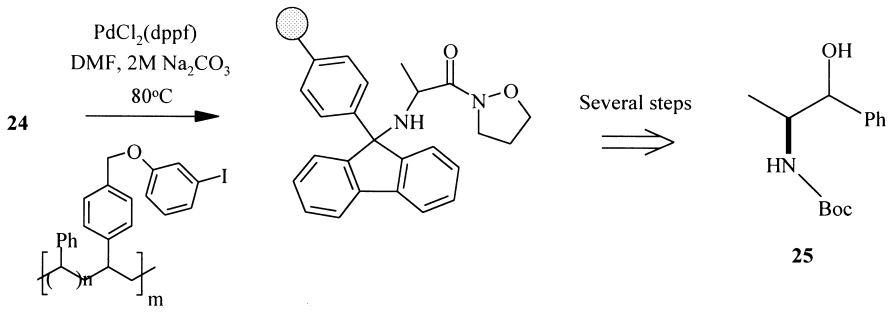
Scheme 14.

than the trityl group[20b] makes the PhF a good linker for the solid phase synthesis of α-amino carbonyl compounds. Alkylation of L-alanine methyl ester with 9-bromo-9-*p*-bromophenyl fluorene **22**, hydrolysis of the ester, and coupling to isoxazolidine provided compound **23** (Scheme 13).

Compound **23** was converted to the corresponding boronate **24** in 92% yield by treatment with diboron pinacol ester, potassium acetate, and $PdCl_2$ (dppf) (Scheme 14). The boronate derivative **24** was then attached to polymeric aryl halides, in good to excellent yields. *N*-(Boc)-norephedrines **25** were produced in 46% overall yield from L-*N*-[*p*-(pinacolboronato)phenylfluorenyl]alanine isoxazolidine **24** (Scheme 15).

Bhawal and coworkers reported the use of the (α-thiophenyl)benzyl group as a novel nitrogen protecting group for the synthesis of *N*1-unsubstituted β-lactams.[21,22] The Staudinger cycloaddition reaction of *N*-(α-thiophenyl)benzyl protected imines **26**, with a variety of acid chlorides, resulted in diastereomeric mixtures of (±)*cis*-β-lactams **27** and **28**, in moderate to good yields.

Nitrogen deprotection was achieved under mild conditions with potassium persulfate to give the desired *N*1-unsubstituted-β-lactam **29** in good yields (Scheme 16). The generality of the (α-thiophenyl)benzyl as a nitrogen protecting group is limited by the need to build this protecting group into the molecule early in the synthesis.



Scheme 15.

The *N*-(α-thiophenyl)benzyl protected imines **26** were prepared in two steps, starting with the required aromatic aldehydes and an excess of ammonia solution, to give 1-phenyl-*N*,*N*′-bis(phenylmethylene)methanediamine **30** in excellent yields,[23] which was then reacted with thiophenol in dioxane to give imines **26** in good yields (Scheme 17).[24]

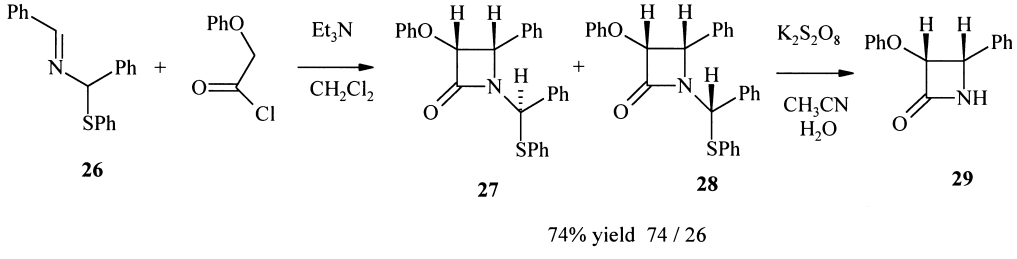
3. Recent Developments and New Applications

3.1. Polyamines

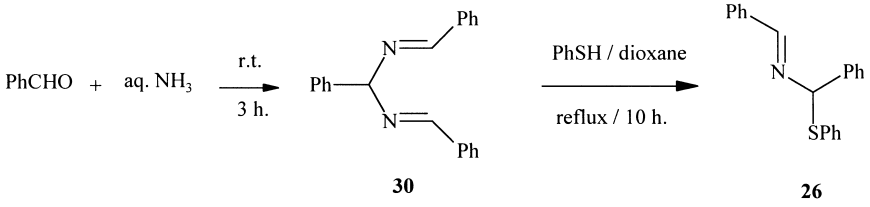
Polyamines, which are widely found in a number of animals, plants, and bacteria,[25–27] have recently attracted a great deal of interest because of their potential as therapeutics;[28] their involvement in DNA, RNA, and protein synthesis;[29] and as a potential source of pharmaceutical and insecticide lead structures.[30] The need for the efficient synthesis of polyamines has sparked a great deal of work in both the design of multiple orthogonal *N*-protecting groups and the selective protection of primary amine functions in the presence of secondary amines.[31,32]

The efficient synthesis of polyamines such as hirudonine **36** was recently achieved by the protection of specific polyamine amino groups as their *N*-trifluoroacetyl or *N*-4-azidobenzyloxycarbonyl derivatives.[33] Selective protection of the primary amine function was achieved by refluxing spermidine **31** with 4 equiv. of ethyl trifluoroacetate and 1 equiv. of water in acetonitrile. This procedure was reported to offer several advantages—such as technical simplicity and readily available reagents—over previously reported methods.[34] N^1,N^8-bis(trifluoroacetyl)-N^4-(4-azidobenzyloxycarbonyl)spermidine **33** was obtained from the reaction of compound **32** with *N*-ethyldiisopropylamine and 4-azidobenzyl-4-nitrophenyl carbonate in THF. The trifluoroacetyl and *N*-4-azidobenzyloxycarbonyl groups were chemoselectively removed by the use of methanolic ammonia, and dithiothreitol-triethylamine, respectively (Scheme 18).

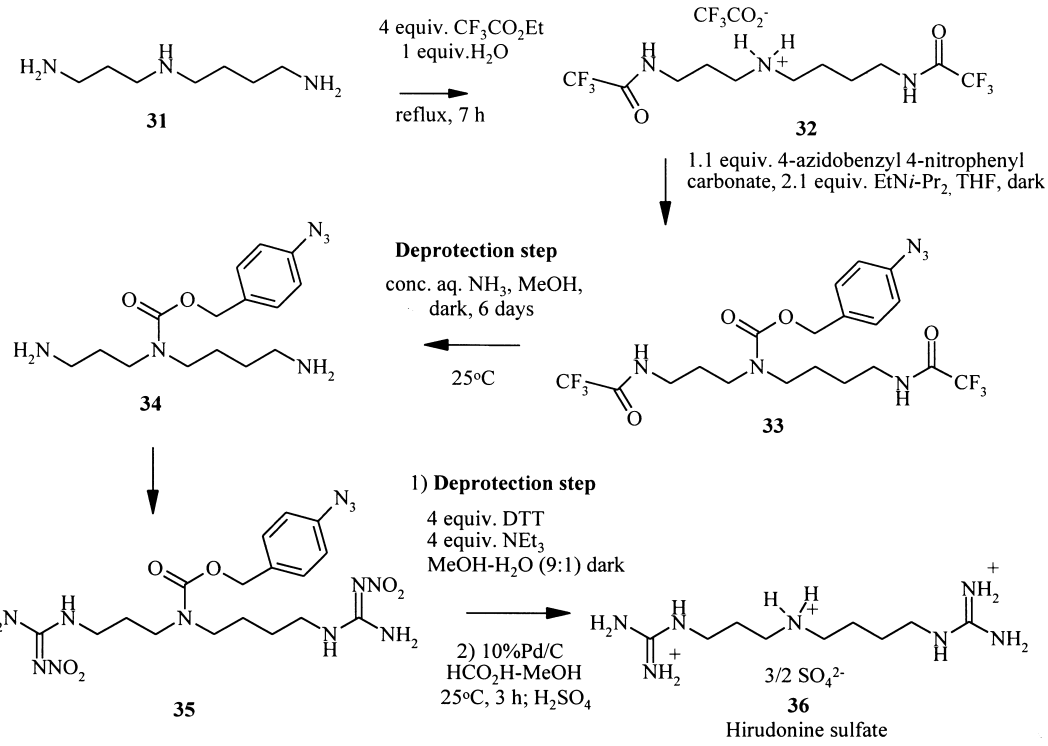
As was mentioned earlier, ethyl trifluoroacetate has found wide application as a selective nitrogen protecting group for primary amines.[35] The use of the *N*-trifluoroacetyl group, which is susceptible to hydrolysis in weak base, is limited to cases where basic media is not required in subsequent reactions. Krakowiak and Bradshaw demonstrated the use of trityl chloride as an alternative protecting group to the trifluoroacetyl group for primary amines when the protected molecule will be subjected to basic reaction conditions.[36] Treatment of linear tetramines **37** with equimolecular amounts of trityl chloride resulted in α,ω-bistrityl protected



Scheme 16.



Scheme 17.

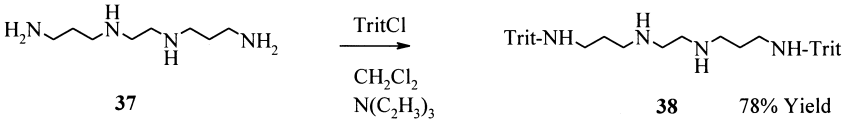


Scheme 18.

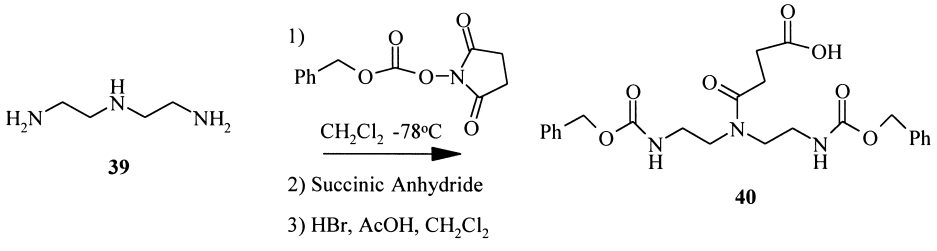
polyamines **38** in good yields (Scheme 19). Yields were based on the amount of trityl used.

A third approach for the chemoselective protection of primary amines, in the presence of secondary amines, is the use of the carbamate protecting group. Differential *N*-protection of polyamines with carbamates was achieved by the use of *O*-alkyl-*O′*-(*N*-succimidyl)carbonates.[37] Low reaction temperatures were important for high yields of the desired product, which could be obtained in a pure form without the need for chromatographic purification. This chemoselective protection strategy was put to practice in the synthesis of compound **40**, a potential molecular scaffold for combinatorial libraries, from diethylene triamine **39** in three steps in 73% overall yield (Scheme 20).

Several studies have recently appeared on the synthesis and derivatization of polyamines obtained from spider venoms.[38–41] Hesse and coworkers have done extensive work in the development of strategies for the synthesis of penta *N*-protected polyamines, containing five independently removable *N*-protecting groups.[38–40] The synthesis of penta *N*-protected polyamine **41** (Fig. 1), and the selective deprotection of the five protecting groups, allyl, azido, (tert-butoxy)carbonyl (Boc), trifluoroacetyl, and [2-(trimethylsilyl)ethyl]sulfonyl (SES), as well as the rapid transamidation reaction of the trifluoroacetyl group yielding secondary amides, was described.[40] The penta *N*-protected polyamine derivative **41** was selectively deprotected and acylated with 4-methoxycinnamoyl chloride on each of the nitrogens (Scheme 21).



Scheme 19.



Scheme 20.

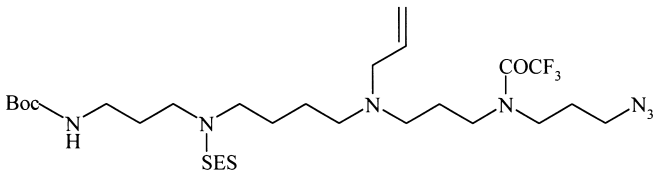


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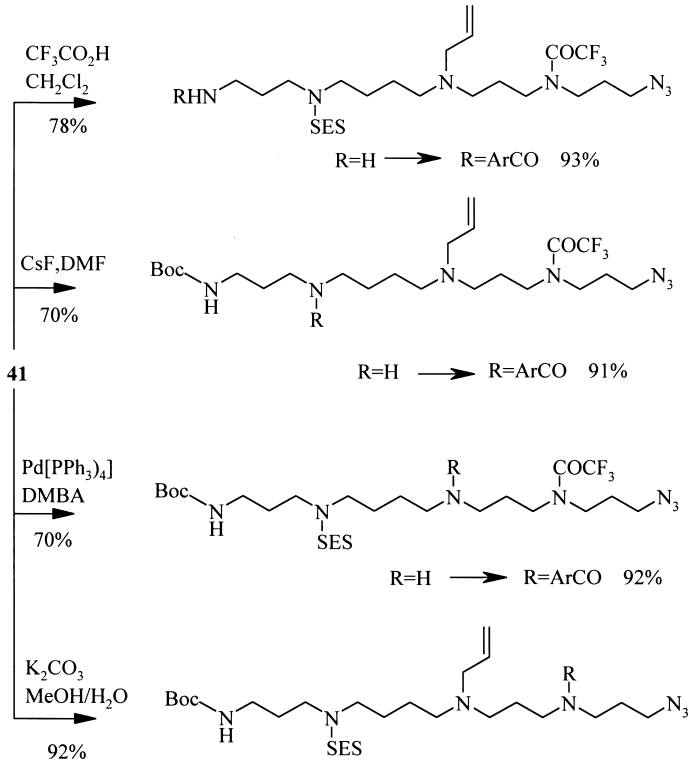
Figure 1.

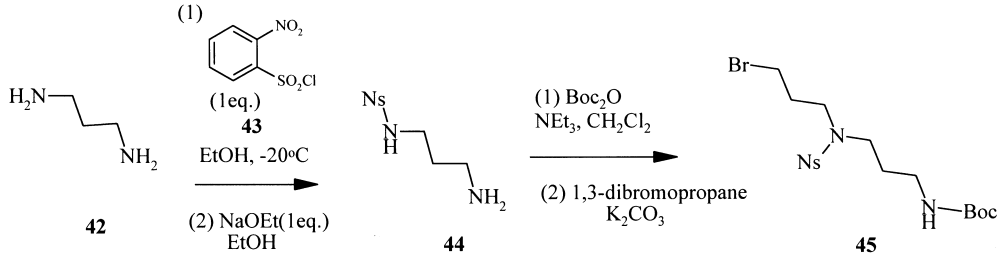


Scheme 21.

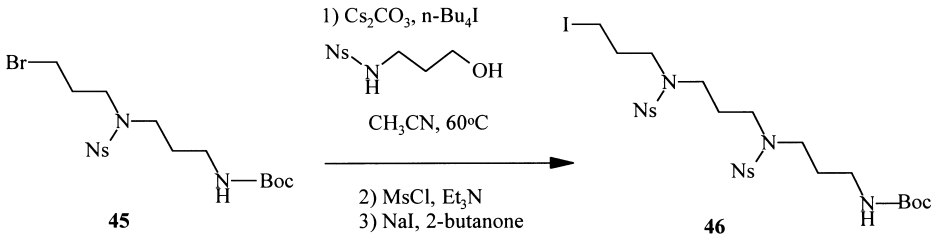
The total synthesis of the polyamine toxin HO-416b **50**, found in spider venom, was recently accomplished in 12 steps and 41% overall yield, employing the 2-nitrobenzenesulfonamide (Ns) group as both a nitrogen protecting and activating group.[41] The mono-nosylated diamines **44**, prepared in good yields from the reaction of the corresponding diamines **42** and 2-nitrobenzesulfonyl chloride **43**, were used as the starting materials for the synthesis of HO-416b **50**. The nosyl group in 1-(2-nitrobenzesulfonyl)amino-3-aminopropane **44** was used not only as a protecting but also as a directing group to allow for the regioselective alkylation of the nosylamide with 1,3-dibromopropane, in 97% yield (Scheme 22).

Reaction of compound **45** with 1-(2-nitrobenzesulfonyl)-amino-3-hydroxypropane gave the polyamine with a terminal hydroxy group, which was subsequently converted to the iodo derivative **46** in two steps (Scheme 23).

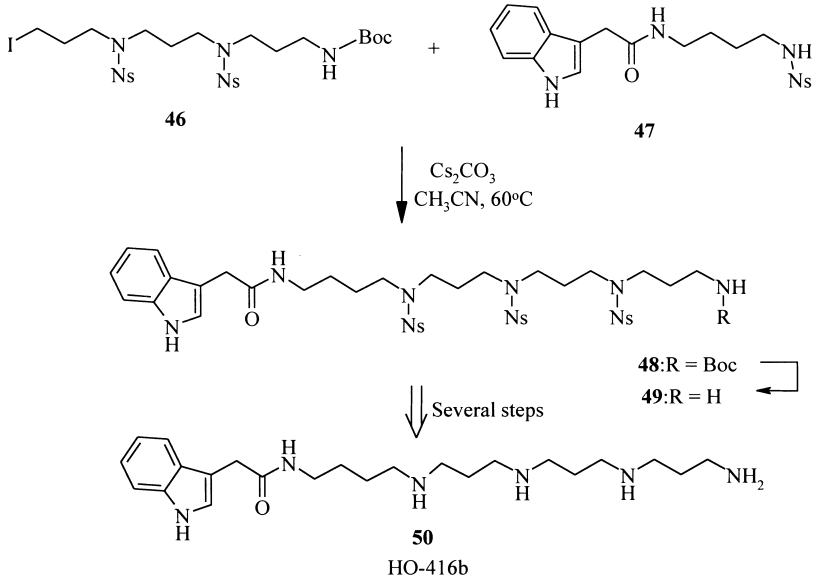
Reaction of iodopolyamine **46** with the indole derivative **47**



Scheme 22.



Scheme 23.



Scheme 24.

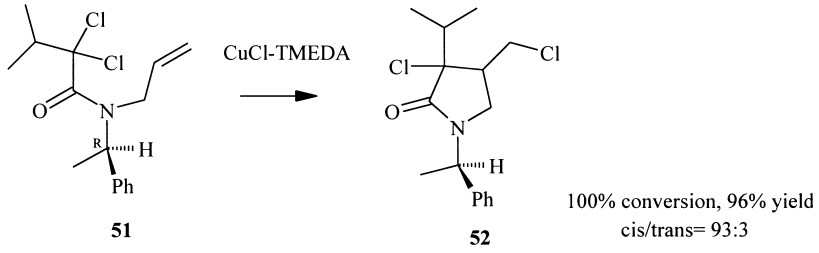
gave the fully *N*-protected pentamine **48**. Removal of the Boc group with methanolic HCl gave the desired primary amine **49**, which was then loaded on an especially prepared trityl chloride resin. Removal of the *N*-nosylate protecting group with mercaptoethanol and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), followed by the cleavage of the product from the resin with trifluoroacetic acid gave the desired polyamine HO-416b **50** (Scheme 24).

3.2. Stereochemical control

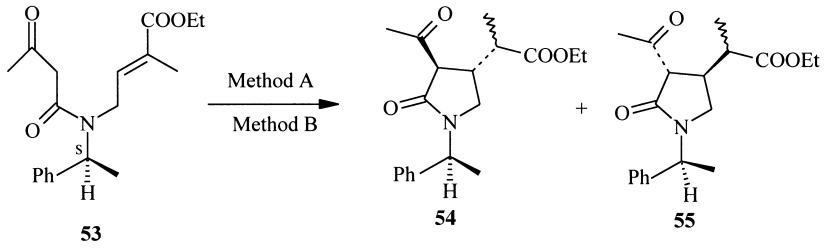
The use of chemical groups that can act as both nitrogen protecting groups and chiral auxiliaries have attracted a great deal of attention. In this respect, the most studied nitrogen protecting group for stereocontrol is the 1-phenylethyl.

3.2.1. 1-Phenylethylamine. Though we have known for some time of the use of chiral 1-phenylethylamine (the two enantiomers of which are readily available) for the asymmetric synthesis of amines,[42,43] it was not until recently that a wider range of applications for this nitrogen protecting group were reported. The *N*-1-phenylethyl group has been used to prepare diastereomerically pure pyrrolidin-2-ones,[44] the stereoselective synthesis of β-lactams,[45–47] chiral α-substituted *N*-[((2*S*)-2-hydroxy-2-phenyl)ethyl]-2-phenylglycine,[48] and chiral 1β-methylcarbapenem intermediates.[49] The lithium salt of (*S*)-(α-methylbenzyl)allylamine and (+)-(camphorsulfonyl)oxaziridine was used for the asymmetric synthesis of β-amino-α-hydroxy acids.[50]

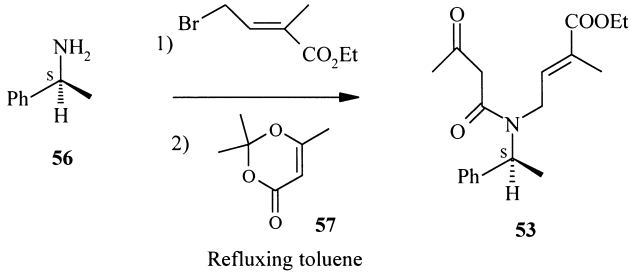
The use of various nitrogen protecting groups in the metal-catalyzed synthesis of γ-lactams has been reported to affect both the rate of reaction[51] and the stereochemistry of the



Scheme 25.



Scheme 26.



Scheme 27.

final product.[51,52] A series of *N*-benzylic protecting groups and allylic substituents were investigated for the CuCl-TMEDA promoted rearrangement of *N*-allyl-2,2-dihaloamides to γ-lactams. Considerable chiral induction was observed at the C-4 position when (*R*)-1-phenylethylamine was used as a chiral *N*-protecting group.[52] The cyclization of *N*-allyl-2,2-dichloroamides **51** requires the presence of a nitrogen protecting group for high yields of atom transfer, resulting in pyrrolidin-2-ones **52** (Scheme 25). The *N*-protecting group forces the amide to assume a conformation with both the alkene and haloalkyl groups on the same side.[53]

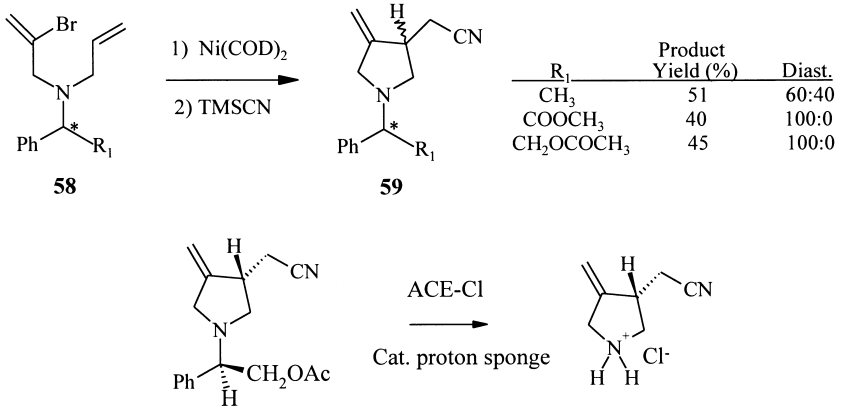
(*S*)-1-Phenylethylamine was previously used as a chiral auxiliary by Orena et al.[44] to prepare diastereomerically pure 1,3,4-trisubstituted pyrrolidin-2-ones by intramolecular cyclization of *N*-(2-alken-1-yl)amides with Mn(III). More recently, the same authors reported a dramatic effect of the reaction conditions on the stereoselective intramolecular conjugate addition of amide enolates to give chiral *trans*-3,4-disubstituted pyrrolidin-2-ones.[54] Treatment of amide **53** with NaH in THF at −78°C gave pyrrolidin-2-one **54** and **55**, in high yield and with good diastereoselection. The main component of the reaction mixture was **55**.

The opposite was observed when sodium ethoxide in ethanol, at −78°C, was used. In this case the main component was **54** (Scheme 26). These results were rationalized on the basis of thermodynamic vs. kinetic control.

The 1-phenylethyl group was introduced from the reaction of (*S*)-1-phenylethylamine **56** with allylic halides, or methanesulfonates, and subsequent treatment with 2,2,6-trimethyl-4H-1,3-dioxin-4-one **57** (Scheme 27).

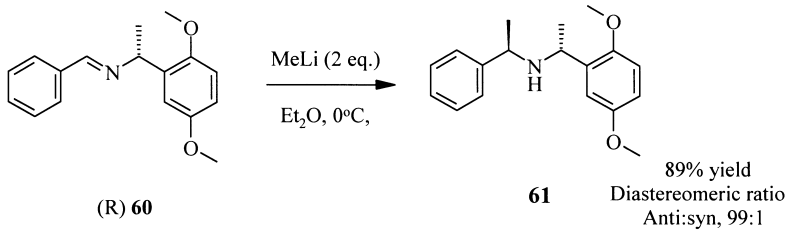
The diastereoselectivity of the nickel-promoted tandem cyclization-quenching of aminobromodienes **58** to give pyrrolidines **59** could be efficiently controlled by the choice of the chiral auxiliary at the nitrogen. In this case the replacement of the α-methyl substituent on the benzyl moiety with groups such as methoxycarbonyl or acetoxymethyl, resulted in complete diastereoselection (Scheme 28).[55] Deprotection was achieved, in one step, by treatment of the pyrrolidine with 1-chloroethyl chloroformate (ACE-Cl).

3.2.2. 1-(2,5-Dimethoxyphenyl)ethylamine. The chiral amine 1-(2,5-dimethoxyphenyl)ethylamine was effectively used as a chiral auxiliary in the diastereoselective alkylation of aldimines **60** with alkyl metals (Scheme 29).[56] This *N*-protecting group was used to overcome earlier difficulties

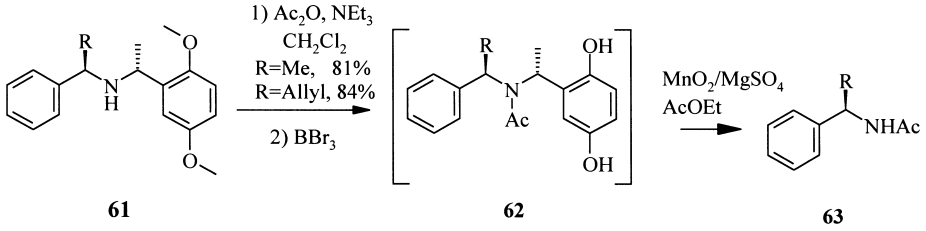


R_1	Product Yield (%)	Diast.
CH_3	51	60:40
$COOCH_3$	40	100:0
CH_2OCOCH_3	45	100:0

Scheme 28.



Scheme 29.



Scheme 30.

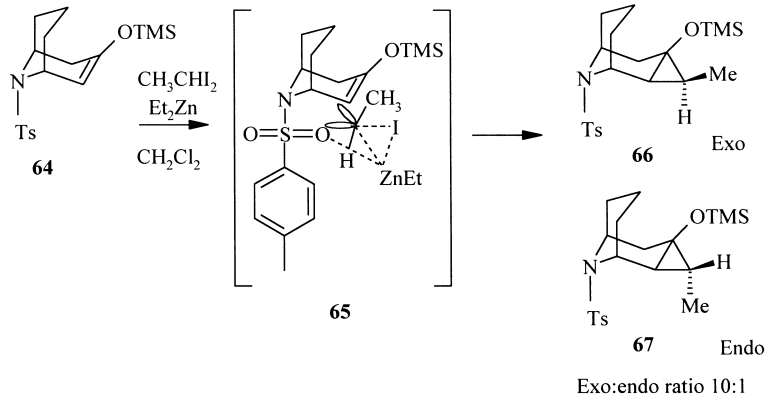
encountered with the deprotection of 1-(2-methoxyphenyl)-ethylamine.[57] Methylation of enantiopure aldimine (R) **60** with methyllithium gave the methylated product **61** in good yields and with excellent diastereoselectivity.

Removal of the 1-(2,5-dimethoxyphenyl)ethyl group was achieved in a three step procedure. Treatment of the *N*-acetylated secondary amine with boron tribromide gave the intermediate hydroquinone **62**, that was oxidized with MnO_2 to give the desired product **63** in acceptable yields, 71% when R=methyl, and 46% when R=allyl, for the last two steps (Scheme 30).

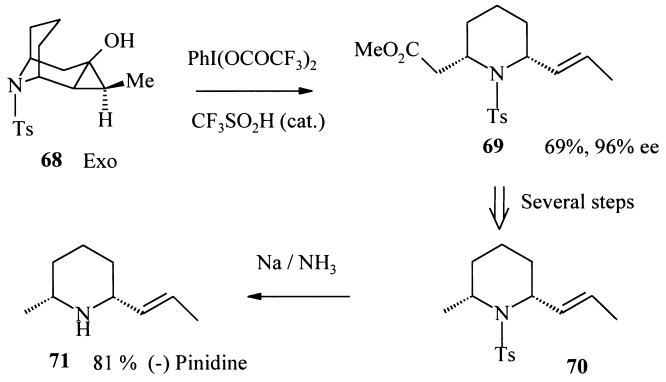
3.2.3. *N*-Sulfonyl group. The effect of a series of *N*-protecting groups on the diastereoselective cyclopropanation of (±)-3-trimethylsilyloxy)-9-azabicyclo-[3.3.1]nonenes **64** was studied.[58] In the cases where the protecting group was an acyl or alkoxycarbonyl, a 1:1 mixture of 3-exo-methyl-4-(trimethylsilyloxy)-10-azatricyclo[4.3.1.0]decanes and the 3-endo compound was obtained. Interestingly, replacement of the previous *N*-protecting groups with a sulfonyl group, such as the methanesulfonyl or *p*-toluenesulfonyl groups, resulted in a dramatic improvement in diastereoselectivity to produce the *exo*-methyl compound **66** predominantly. This finding was rationalized by coordination of the sulfonamide oxygen with the zinc on the carbenoid **65**, which then attacks the double bond in a less hindered fashion, as shown in Scheme 31.

The desilylated *exo* compound **68** was subjected to oxidative ring cleavage with hypervalent λ^n-iodane, phenyliodine(III) bistrifluoroacetate (PIFA), to give the (E)-alkene **69** stereospecifically. Following reduction and decarbonylation, compound **70** was obtained, which was then deprotected with Na/liquid NH_3 in ethanol at −78°C to give (−)-pinidine[59] **71** in 81% yield (Scheme 32).

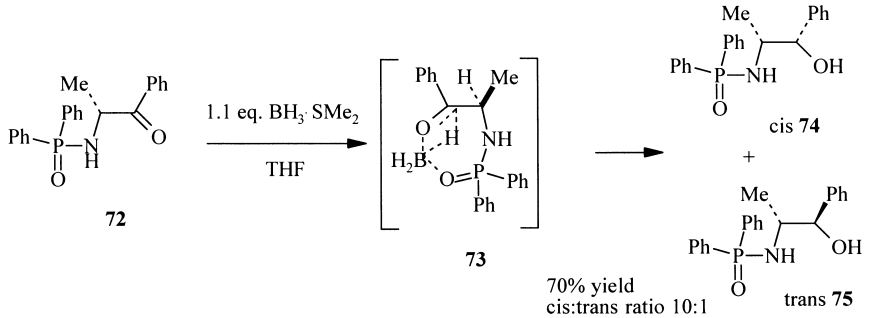
3.2.4. *N*-Phosphinamide group. Though phosphinamides have previously been used as nitrogen protecting groups, first by Ramage and coworkers[60] and later by Sweeney and coworkers,[61] their use has not gained wide acceptance. Wills and coworkers have reported the use of phosphinamides as catalysts in the asymmetric reduction of ketones by borane.[62] More recently, Wills et al. has reported the use of the *N*-diphenylphosphinyl group as both a protecting group and a directing group for the diastereoselective synthesis of β-amino alcohols.[63] Reaction of compound (*R*)-**72** with a stoichiometric amount of borane–dimethylsulfide complex gave alcohols **74** and **75**, as a 10:1 ratio of diastereoisomers. The authors proposed that the observed diastereoselectivity



Scheme 31.



Scheme 32.



Scheme 33.

is a result of the phosphinamide group directing the reduction by means of transition state complex **73** (Scheme 33). The *N*-diphenylphosphinyl group is readily removed with dilute acid.[60]

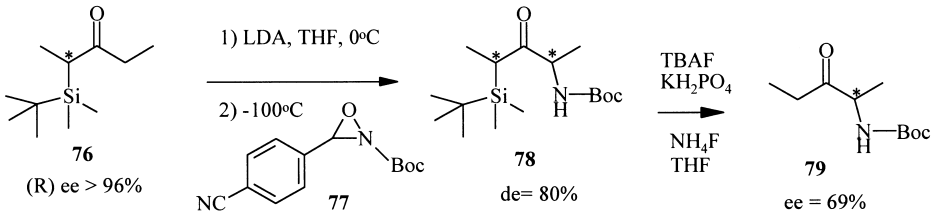
3.2.5. Oxaziridine. Synthesis of α-aminocarbonyl compounds, via the electrophilic α-amination of carbonyl molecules continues to attract a good deal of attention.[64] The asymmetric synthesis of *N*-Boc protected α-aminoketones was recently achieved via the *N*-Boc-3-(4-cyanophenyl)oxaziridine **77** electrophilic amination of enantiopure α-silyl ketones, followed by the removal of the silyl directing group with tetrabutyl ammonium fluoride.[65]

The ketones were converted to the corresponding enantiomerically pure α-silylketones **76** by known procedures.[66] Treatment of the α-silylketones **76** with diisopropylamide (LDA) at 0°C resulted in the formation of the corresponding enolate, which was reacted with the oxaziridine **77** to give the α-aminated α′-silyketone compound **78**. Finally, to avoid racemization of the α-aminoketone, cleavage of the silyl directing group required the use of the appropriate temperature and buffer system. Best results were obtained at −78 to −20°C with TBAF and a buffer solution of NH_4F, KH_2PO_4, HF. The *N*-Boc protected α-aminoketones **79** were obtained in moderate yields and *ee*-values (Scheme 34).

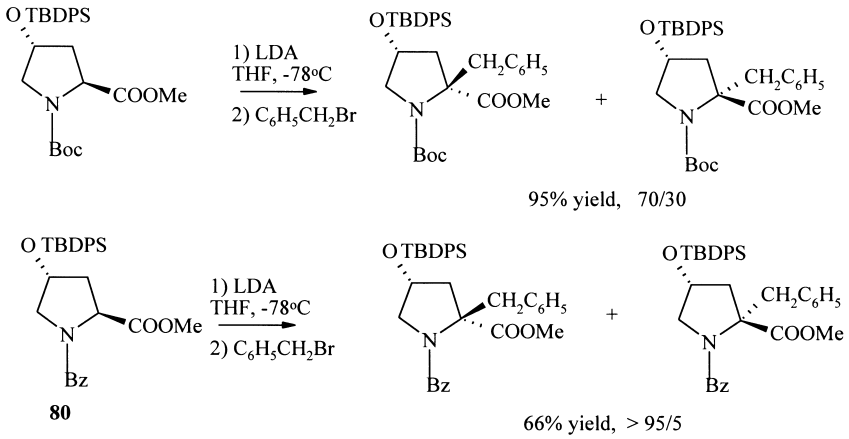
3.2.6. *N*-Benzoyl group. The diastereoselectivity of products obtained from the alkylation of *N*-protected -4-hydroxyproline was found to be dependent on both the alkylating reagent and the choice of the nitrogen protecting group.[67] Both the Boc and benzoyl groups were investigated. Highly selective benzylation was obtained when the 4-hydroxyproline nitrogen was protected with a benzoyl group, compound **80** (Scheme 35). These results were rationalized on the basis of the stereoelectronic effect and π-interactions.

3.3. Deprotection

3.3.1. Enzymatic deprotection. The ability of enzymes to carry out chemoselective and regioselective chemical reactions, under either neutral, weakly acidic, or weakly basic conditions, offers a very attractive alternative to chemical means of nitrogen deprotection. A review by



Scheme 34.



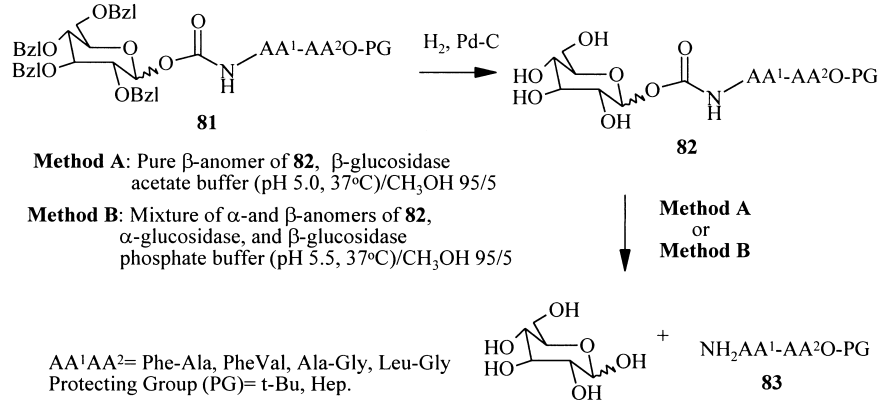
Scheme 35.

Pathak and Waldmann[68] covers the recent literature in this area from 1996 to early 1997.

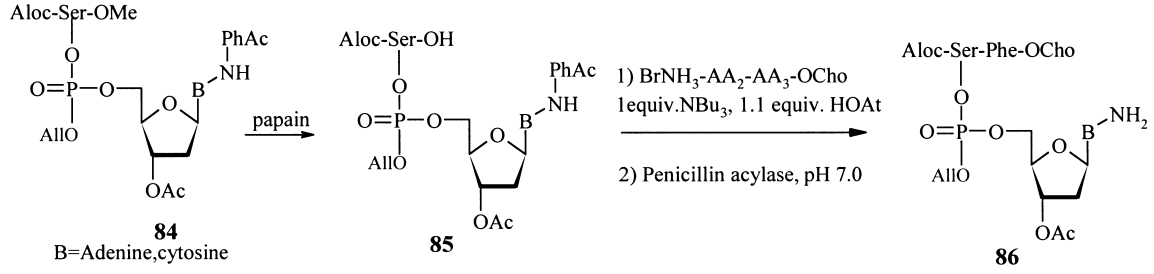
A new, enzymatically removable nitrogen protecting group for peptide synthesis was reported by Kappes and Waldmann.[69] The urethane type protecting group, tetra-benzylglucosyloxycarbonyl (Bgloc), has a carbohydrate ester linkage, compound **81**, which is readily removed in two steps: hydrogenolysis of the benzyl ethers followed by hydrolysis of the urethane function in **82** with α- and β-glucosidase enzymes (Scheme 36).

Nucleopeptides were efficiently constructed by using different enzymatic protecting group techniques for the selective deprotection of various functional groups present, such as carboxylic acids, nucleobases, and hydroxy groups.[70] The exocyclic amino group of the nucleobase **85** was selectively *N*-deprotected by the enzyme penicillin acylase, which catalyzed the removal of the phenylacetamido group to give **86** in 82% yield (Scheme 37).

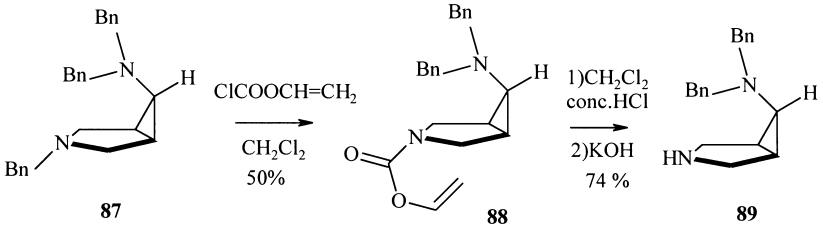
The reactivity of the phenylacetyl (PhAc) and mandelyl (Mand) protecting groups to enzymatic deprotection in peptide synthesis was recently investigated for the papain-catalyzed condensation between *N*-α protected esters of glycine and H-Trp-Obzl.[71] PhAc-Gly-OCam and Mand-Gly-Obzl gave good yields using papain and synthetic yields similar to those of Z-Gly-Ocam, but higher than those of Boc-Gly-Ocam derivatives.



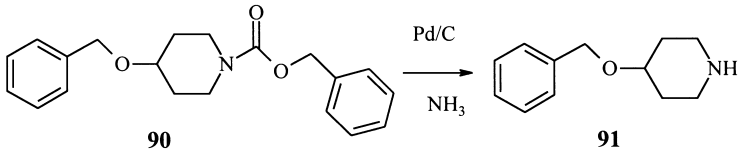
Scheme 36.



Scheme 37.



Scheme 38.



Scheme 39.

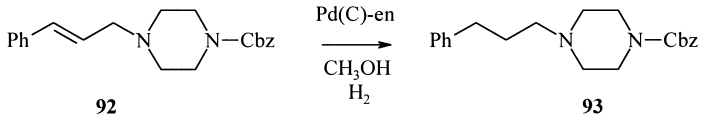
3.3.2. Selective debenzylation. The selective removal of only one of several identical nitrogen protecting groups in a molecule has recently been achieved. A selective debenzylation of compound **87**, containing three *N*-benzyl groups, by the use of vinyl or methyl chloroformate has been reported.[72] Initial attempts to selectively deprotect the benzyl group at the secondary nitrogen of compound **87** by catalytic hydrogenolysis with 1 equiv. of hydrogen, and a palladium/charcoal catalyst, resulted in a mixture of several debenzylated products. A selective debenzylation was achieved when compound **87** was reacted with vinyl chloroformate in chloroform to give the corresponding carbamate **88** in 50% yield. Treatment of compound **88** with hydrochloric acid resulted in removal of the carbamate group to give the deprotected amine **89** (Scheme 38). In addition to vinyl chloroformate, methyl chloroformate was also used to selectively deprotect the benzyl group at the secondary nitrogen.

A chemoselective debenzylation was also achieved by the addition of a nitrogen-containing base during the hydrogenolysis of *O*-benzyl containing molecules such as **90** (Scheme 39).[73] In the absence of the additive nitrogen-containing base, the benzyl ether group was easily removed to produce the corresponding alcohol in excellent yields.

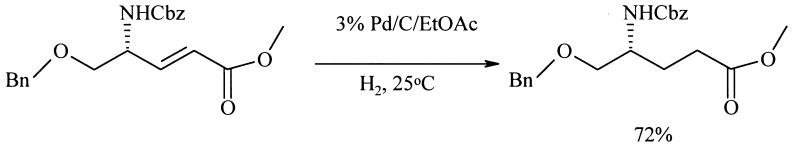
In addition to the selective debenzylation reactions discussed previously, several methods for the chemoselective hydrogenation of functionalities in the presence of benzyl protecting groups have appeared recently. The versatility of the benzyloxycarbonyl (Cbz) protecting group has been further extended by two recent studies, the first of which used a Pd/C–ethylenediamine complex catalyst to allow for the chemoselective hydrogenation of a variety of functionalities such as olefins, acetylene, azido, benzyl ester, and nitro without affecting the *N*-Cbz protecting group (Scheme 40).[74] For instance, treatment of compound **92** with Pd (carbon)-en resulted in the chemoselective hydrogenation of the olefin to give the *N*-Cbz protected compound **93**.

The second chemoselective approach involved the use of 3% Pd/C in ethyl acetate; though the selectivity towards benzyl ethers and benzyl esters was good, the selectivity towards the *N*-benzyloxycarbonyl protecting group was only moderate (Scheme 41).[75]

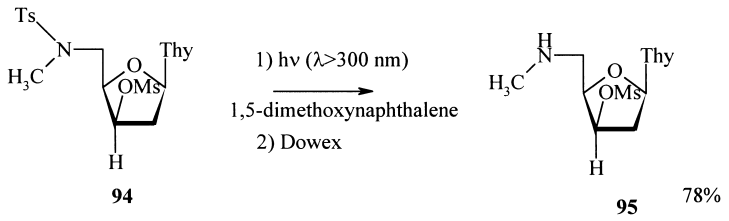
3.3.3. Photochemical deprotection. The selective photohydrolysis of 5′-*N*-tosylamide **94** was successfully carried out by the use of UV irradiation (>300 nm), in the presence of 1,5-dimethoxynaphthalene as an electron donor (Scheme 42). This novel deprotection approach to the *N*-tosyl groups in nucleosides should find use where the more common deblocking conditions of either strong base, or strong acid, are not appropriate.[76]



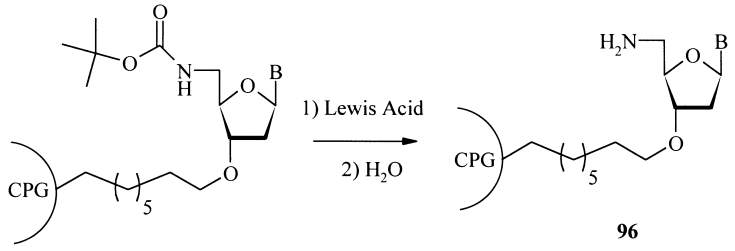
Scheme 40.



Scheme 41.

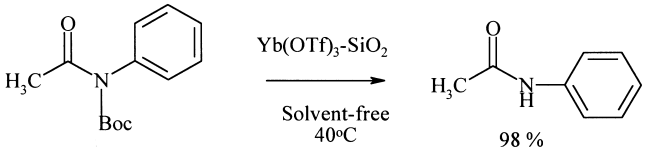


Scheme 42.



Scheme 43.

3.3.4. Lewis acids. The potential of Lewis acids to deprotect alkyl and benzyl esters had been known.[77] Several recent papers report the use of various Lewis acids for the deprotection of molecules containing nitrogen protecting groups. Two of these publications describe the use of aluminum chloride, as the Lewis acid, to remove the Boc protecting group.[78,79] In one case, during solid phase oligonucleotide synthesis, deprotection of the Boc group with $AlCl_3$ gave quantitative yields of the corresponding primary amine **96** (Scheme 43). The presence of anisole was essential to the reaction, because of the thymidine instability to $AlCl_3$.[78] This procedure avoids the use of strong acids such as trifluoroacetic acid for the removal of the Boc group.



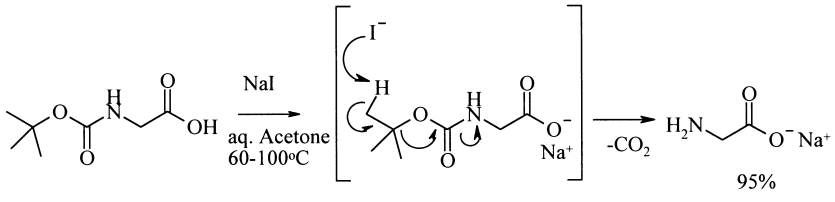
Scheme 44.

The Boc group was also removed by the Lewis acid $Yb(OTf)_3$ supported on silica gel, under solvent-free conditions in excellent yields (Scheme 44).[80]

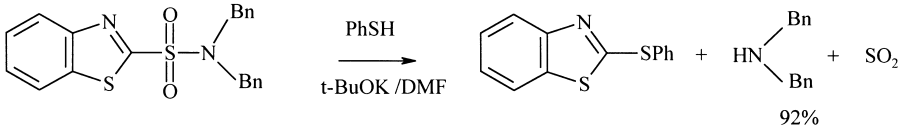
3.3.5. Sodium iodide. The Boc group was removed on refluxing in aqueous acetone in the presence of sodium iodide.[81] The proposed mechanism is shown below (Scheme 45). The reaction is fast—generally being over in less than 30 min—mild, and high yielding.

Wuts et al. reported the use of thiols in the deprotection of benzothiazolesulfonamides (Bts). Thiophenol, as well as the less malodorous dithiothreitol (DTT), was used to affect the deprotection, which takes place under mild, nonacidic conditions (Scheme 46).[82]

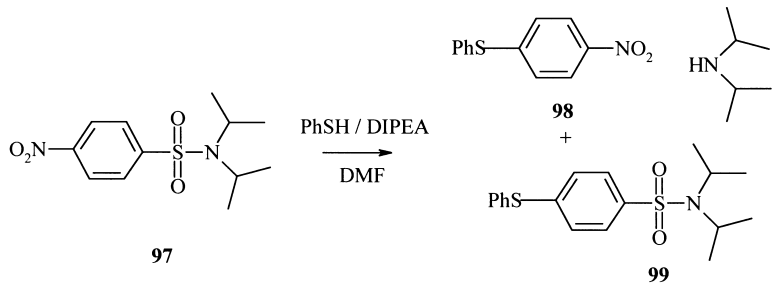
The same group has cautioned about the use of thiolate to deprotect *p*-nitrobenzenesulfonamides. Apparently, during the cleavage of the *p*-nitrobenzenesulfonamide group with thiophenol, replacement of the nitro group occurred, to give the side product **99** in yields ranging from 4–19% (Scheme 47). The side reaction tends to occur to a larger extent with cyclic amines, possibly because of steric requirements.[83]



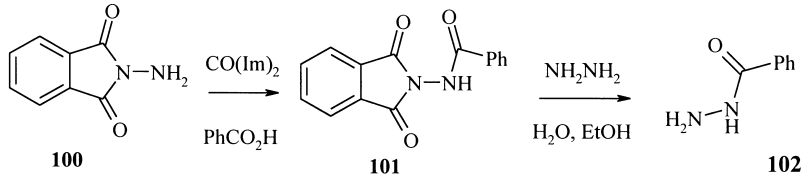
Scheme 45.



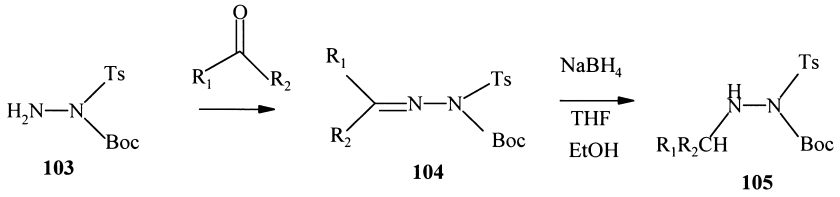
Scheme 46.



Scheme 47.



Scheme 48.



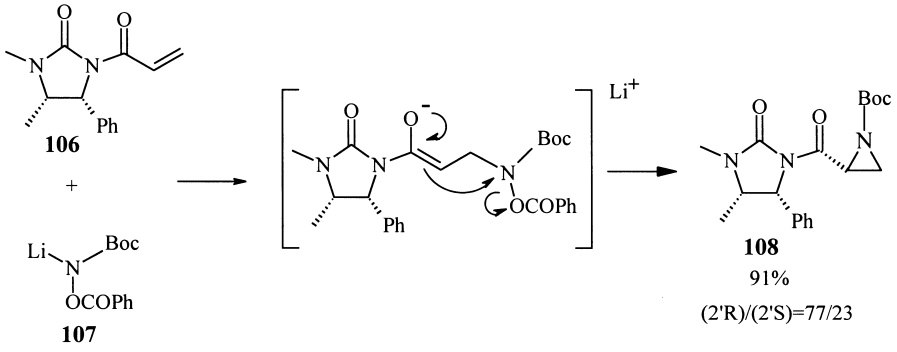
Scheme 49.

3.4. Miscellaneous

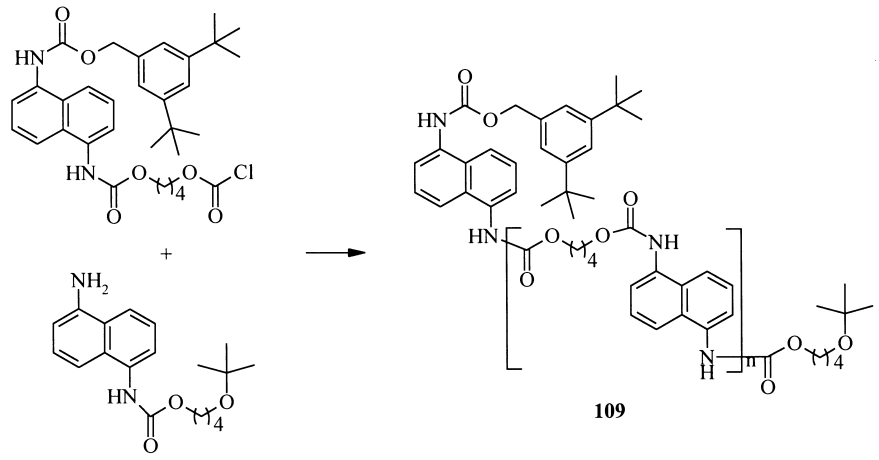
3.4.1. Hydrazines. The synthesis of protected hydrazines constitutes an important part of organic chemistry because of the utility of mono- and diprotected hydrazines in the preparation of heterocyclic compounds[84,85] and azapeptides.[86,87] Two recent reports on the preparation of *N*-(substituted) and *N*,*N*-bis(substituted) hydrazines have appeared. In the first case, acylation of *N*-aminophthalimide **100** by a number of acids, such as acetic, benzoic, and pyvaloic acids, was achieved by using 1,1′-carbonyl-diimidazole, $CO(Im)_2$, as activating agent. Removal of the phthaloyl group by treatment of **101** with hydrazine hydrate (Scheme 48)[88] gave the desired benzoic hydrazide **102** in 68% yield.

The second procedure provides a methodology for the synthesis of *N*-(secondary alkyl)-*N*,*N*-bis(protected)-hydrazines **105** from the reaction of *N*,*N*-bis(protected)-hydrazines **103** and a ketone, to give the intermediate hydrazone **104**. Reduction of **104** with $NaBH_4$ gave the desired *N*-(secondary alkyl)-*N*,*N*-bis(protected)hydrazines, having two orthogonal protecting groups, in good yields (Scheme 49).[89,90]

Chiral aziridine **108** was obtained in a one-step procedure,



Scheme 50.



Scheme 51.

which involved conjugate addition–cyclization of *N*-Boc-*O*-benzoylhydroxylamine **107** to an α,β-unsaturated chiral imide **106** in 91% yield, and an isolated yield of a 77/23 diastereomeric ratio in favor of the 2′-R isomer (Scheme 50).[91] For best results, the reaction requires 2 equiv. of base, in this case BuLi, and 2 equiv. of the bis(protected) amine.

Two recent reports described the improved versatility of existing nitrogen protecting groups, through the presence of different additives to modify the stability of the protecting groups. In the first case, complete orthogonality between the 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl (Dde) and allyloxycarbonyl (alloc) *N*-protecting groups was achieved, in the hydrazinolysis of Dde, by the addition of allyl alcohol.[92] In general, removal of the Dde group by hydrazine, in peptides containing both Dde and Alloc groups, results in partial reduction of the Alloc double bond. The addition of allyl alcohol as a scavenger completely prevents the hydrogenation of the Alloc group. The second report referred to the improved stability of the Fmoc protective group in peptide synthesis, under alkaline conditions, by the addition of $CaCl_2$. This allows for the preparation of Fmoc-protected peptide segments by basic hydrolysis of the corresponding C-terminal methyl and benzyl esters.[93]

3.4.2. Protecting groups in polymer synthesis. The use of protecting groups in polymerizations has recently been reviewed.[94] The use of oxygen and nitrogen protecting groups facilitates the synthesis of functional polymers. One such example is the use of 3,5-di-*tert*-butylbenzyloxycarbonyl (3,5-di-*t*BBOC) group, which was found to significantly improve the solubility of intermediates for polymerizations, over the benzyloxycarbonyl group (Cbz).[95]

Solubility issues restricted the stepwise building up of 1,5-naphthalene diamine (NDA)-based oligourethanes **109**—involving the cleavage of the Cbz group and subsequent reaction—to a maximum of two NDA/1,4-butanediol (BDO) repeating units. The improved solubility properties, gained from the replacement of Cbz with 3,5-di-*t*BBOC, allowed for the stepwise building up of oligourethane model compounds (Scheme 51), as well as considerable improvements in the purification of intermediates.

4. Summary

Continued interest in the protection of the nitrogen functionality in a variety of molecules has resulted in a number of both new protecting groups and new applications for already established protecting groups. These new advances should provide researchers with additional tools for the building of complex molecules. The ability of some nitrogen protecting groups to dramatically influence the stereochemistry of the final product should continue to be exploited in the design of chiral molecules. Further development of enzymatic deprotection techniques, as well as the specific design of protecting groups for enzymatic deprotection, should offer chemists a wider set of nitrogen protecting alternatives. Finally, a number of the new developments in the protection of nitrogen that have been described in this review could also be of use in the design of linkers in solid phase chemistry.

Acknowledgements

The author would like to thank the reviewers for their comments and suggestions, and Janet Stern for help in the preparation of this manuscript.

Appendix A

A.1. List of protecting group abbreviations

All: Allyl; **Alloc** (or **Aloc**): Allyloxycarbonyl; **Bgloc**: tetrabenzylglucosyloxycarbonyl; **Bn** (or **bzl**): Benzyl; **Boc**: *tert*-Butyloxycarbonyl; **BrPhF**: 9-(9-*p*-Bromophenyl-fluorene); **BrPhF-Br**: 9-Bromo-9-*p*-bromophenylfluorene; **Bts**: Benzothiazolesulfonamides; **Bz**: Benzoyl; **Cbz**: Benzyloxycarbonyl; **Dde**:1-(4,4-Dimethyl-2,6-dioxocyclo-hexylidene)ethyl; **DMPOC**: 1,1-Dimethyl prop-2-ynyloxy carbonyl; **DNPSO$_2$EOC**: 2-(2,4-Dinitrophenylsulfonyl)-ethoxycarbonyl; **Fmoc**: 9-Fluorenylmethoxycarbonyl; **Mand**: Mandelic; **Ns**: 2-nitrobenzenesulfonamide; **PhAc**: Phenylacetyl; **PhF**: 9-Phenylfluorene-9-yl; **Proc**: propargyloxycarbonyl; **SES**: [2-(Trimethylsilyl)ethyl]sulfonyl; **TBDPS**: ***tert*-Butyldiphenylsilyl; TIPS**: Triisopropylsilyl;

TIPS-OTf: Triisopropylsilyl triflate; **TMS**: Trimethylsilyl; **Tsoc**: Triisopropylsilyloxycarbonyl; **Trityl**: Triphenylmethyl.

A.2. Reviews

In addition to general reviews on protecting groups[10,13] and some more specific reviews on nitrogen protecting groups, such as Allylic Protecting Groups,[1] Natural Polyamine Derivatives, [25] Enzymes and Protecting Group Chemistry,[68] and the Use of Protecting Groups in Polymerization,[93] the following reviews proved particularly comprehensive:

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Biographical Sketch

George Theodoridis studied at Leeds University, UK, where he received his B.Sc. degree in chemistry in 1975, and M.Sc. degree in Food Chemistry in 1976. He received his doctorate in Heterocyclic Chemistry in 1980 from the Rensselaer Polytechnic Institute, Troy, New York, under the supervision of Professor Kevin T. Potts. At RPI, with the aid of a Corning Glass Foundation Fellowship, he studied novel applications of ketene dithioacetals in the synthesis of heteromacrocycles, such as substituted hexapyridines. In 1980 he joined the FMC Corporation, in Princeton, NJ, where he worked in the development of new protoporphyrinogen oxidase (Protox) inhibiting herbicides. This research resulted in the discovery of the commercial product sulfentrazone. Other areas of research include the development of heterogeneous catalysts for the selective reduction of polynitrophenyl compounds, novel synthesis of heterocycles utilizing the Meerwein reaction, and more recently the development of new nitrogen protecting groups.